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Title of Thesis: "Psychosocial Factors Versus Single Predictors: A
Factor Analytic Approach to Cardiovascular
Outcomes in The Women's Ischemia Syndrome
Evaluation (WISE) Study"

Name of Candidate: Kerry S. Whittaker
Medical and Clinical Psychology
Master of Science
February 18, 2010

Thesis and Abstract Approved:

David S. Krantz, Ph.D.
Department of Medical and Clinical Psychology
Thesis Advisor

Date

Andrew Waters, Ph.D.
Department of Medical and Clinical Psychology
Committee Member

Date

Ann Scher, Ph.D.
Department of Preventive Medicine and Biometrics
Committee Member

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Date

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A FACTOR ANALYTIC APPROACH TO CARDIOVASCULAR OUTCOMES IN
THE WOMEN'S ISCHEMIA SYNDROME EVALUATION (WISE) STUDY

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A handwritten signature in black ink, appearing to read 'Kerry S. Whittaker', with a stylized, flowing script.

Kerry S. Whittaker
Department of Medical and Clinical Psychology
Uniformed Services University
February 16, 2010

Abstract

Title of Thesis: PSYCHOSOCIAL FACTORS VERSUS SINGLE PREDICTORS:
A FACTOR ANALYTIC APPROACH TO CARDIOVASCULAR OUTCOMES IN
THE WOMEN'S ISCHEMIA SYNDROME EVALUATION (WISE) STUDY

Thesis Advisor: David S. Krantz, Ph.D.

Professor & Chair

Department of Medical and Clinical Psychology

Introduction: Cardiovascular disease (CVD) is the leading cause of death among women in all developed countries (Rosamond, et al., 2008). There are important gender differences in the onset, diagnosis, and progression of CVD, particularly coronary artery disease (CAD). In addition to the traditional health-related risk factors for CAD, a variety of psychosocial variables play a role in the etiology, onset and progression of CAD.

Additionally, many of these psychosocial variables co-occur and cluster in the same individuals, and research suggests that several psychosocial variables overlap (i.e., share variance). Relatively few studies have examined these issues in women. **Methods:** Data were analyzed from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study (Merz, et al., 1999). Principal components factor analysis with varimax rotation was conducted to examine the clustering of psychosocial factors and Cox proportional hazards regressions were used to evaluate the predictive value of these factors for adverse cardiovascular (CV) events (stroke, myocardial infarction, congestive heart failure, and cardiovascular related death).

Results: Factor analysis of psychosocial scales (including BDI, STAI, SNI, Cook-Medley, and measure of panic and autonomic perception) revealed 3 underlying factors (Eigenvalues > 1): Negative Affectivity, Hostility, and Social Support. In a disease-adjusted Cox regression model, the Social Support factor (consisting primarily of the SNI) was protective against CV events (HR: 0.78, 95% CI 0.61-0.99). In Cox regression

analysis the addition of a block including the individual psychosocial variable (a multivariate approach), was a significant addition to the model ($\chi^2 [10]=71.51$, $p<0.001$).

Conclusions: Factor analysis of multiple psychosocial scales yielded 3 factors: Negative Affectivity, Hostility, and Social Support. The Social Support factor was protective against CV events in women with suspected CAD. Evaluating the shared variance of psychosocial variables in a multivariate and/or factor analytic approach may provides valuable information in the prediction of cardiovascular events in women with suspected coronary artery disease.

PSYCHOSOCIAL FACTORS VERSUS SINGLE PREDICTORS:
A FACTOR ANALYTIC APPROACH TO CARDIOVASCULAR OUTCOMES IN
THE WOMEN'S ISCHEMIA SYNDROME EVALUATION (WISE) STUDY

By
Kerry S. Whittaker

Medical and Clinical Psychology Graduate Program
Uniformed Services University of the Health Sciences

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Introduction

Cardiovascular Disease

The term cardiovascular disease (CVD) refers to a number of conditions which affect the heart and blood vessels (e.g., ischemia, coronary artery disease, stroke, and hypertension). Atherosclerosis, a process by which the artery walls thicken, leads to a variety of adverse cardiovascular outcome, such as stroke and myocardial infarction (MI), and accounts for almost three quarters of CVD deaths(Rosamond, et al., 2008). As atherosclerosis advances, plaque builds up inside the coronary arteries, reducing blood flow, a condition commonly known as coronary artery disease (CAD). Cardiovascular disease is the leading cause of death among adults in the industrialized world. In 2005, cardiovascular disease affected over 80 million Americans with 409,900 men and 454,600 women dying as a result of cardiovascular disease(Rosamond, et al., 2008).

There are many biological and psychosocial factors that influence the etiology and progression of CAD. The present study examines the clustering of psychosocial variables and the existence and predictive power of psychosocial factors in women with suspected coronary artery disease. Before presenting the study purpose and hypotheses, a brief review of coronary artery disease and major cardiovascular endpoints will be conducted. Next, some of the gender differences present in CAD will be discussed. Then the relationship between psychosocial variables and CAD will be explored. Finally, a review of psychosocial factors predicting cardiovascular outcomes will be examined and a rationale for the current study aims will be presented.

Progression of Coronary Artery Disease

Atherosclerosis

One of the most important underlying causes of CAD is atherosclerosis, a disease affecting arterial vessels, caused by the formation of plaque within the arteries. The lesions of atherosclerosis occur primarily in the larger muscular arteries. When these lesions become advanced they can result in ischemia of the heart, brain, or extremities, which can lead to infarction (Ross, 1999). The early stages of atherosclerosis are often asymptomatic and because of this often go undiagnosed.

In advanced stages of atherosclerosis a fibrous plaque covers the atherosclerotic lesion. At this stage of the disease a significant decrease in luminal space is usually observed. The atherosclerotic lesion has become far enough advanced that vascular remodeling can no longer compensate for the narrowing lumen, and symptoms of ischemia (see below) often develop. The fibrous plaque can be stable (i.e., if the fibrous cap covering the lesion is sufficiently thick and has developed uniformly) (Ross, 1999). However if the fibrous cap is thin or if there are sections of the surface that are uneven, the plaque can become dangerously unstable and rupture. Plaque rupture can cause the development of thrombus at the site of the plaque rupture leading to arterial occlusion which can result in severe ischemia, myocardial infarction and even sudden death.

Myocardial Ischemia

Myocardial ischemia refers to the imbalance between blood supply and demand in the myocardium, resulting in insufficient oxygen supply to the myocardial tissue. This disrupts the metabolic processes in the myocardium, and when prolonged can result in

tissue damage or even tissue death. In some individuals, ischemia results in no outward physical symptoms. This is known as silent ischemia. Oftentimes ischemia manifests with severe chest pain or discomfort known as angina pectoris. Many patients report feeling pressure, heaviness or tightness in their chest, which is sometimes accompanied by shoulder, neck or jaw pain. Stable angina occurs when these symptoms present with exertion and diminish at rest. If the symptoms occur at rest, or increase markedly in frequency and intensity, the angina is considered unstable and may signal an impending heart attack. Even if the angina is stable, symptoms of ischemia can greatly impact a patient's quality of life and lead many patients to seek medical care.

Myocardial Infarction

Commonly referred to as a heart attack, myocardial infarction (MI) occurs when part of the myocardial tissue dies as a result of lack of blood supply. The interruption in blood supply to the heart tissue is most often caused by an occlusion or blockage of one of the coronary arteries by a ruptured atherosclerotic plaque. Once these myocardial cells die, they are unable to conduct the electrical impulses responsible for heart muscle contraction. If the area of dead myocardial tissue is small, no real disruption in the electrical conduction system of the heart may be seen. If, however there is a large area of dead myocardial tissue or the dead tissue is located in an area critical to the path of electric conduction, a lethal arrhythmia may occur. Research shows that individuals who have had at least one previous MI are 4 to 6 times more likely to die of sudden cardiac death than the general population (Rosamond, et al., 2008). Women are more likely to die in the weeks following an MI than men (See below) (Rosamond, et al., 2008).

Stroke

Similar to a myocardial infarction, a stroke is caused by the interruption of blood supply to all or part of the brain. This interruption in blood supply can be caused by a number of factors such as thrombosis, embolism or a hemorrhage. Stroke is one of the outcomes associated with arteriosclerosis. Just as an atherosclerotic plaque can rupture and occlude a coronary artery, a ruptured plaque can travel through the vasculature to the brain, occluding the vessel and causing an embolism. Stroke is the leading cause of serious long-term disability in the United States (Rosamond, et al., 2008). On average 60,000 more women than men suffer strokes every year (Rosamond, et al., 2008).

Congestive Heart Failure

Congestive heart failure (CHF) is a condition in which the heart is unable to pump enough blood for the body's demands. Congestive heart failure can be the end result of a variety of conditions, such as coronary artery disease, MI, hypertension, congenital defects, alcoholism, and/or infection. Since the heart continues to work unsuccessfully to meet the demands of the body, it becomes enlarged. In patients with heart failure the heart tissue becomes so enlarged that it is no longer able to pump blood effectively. This leads to a severe decrease in blood supply to the body's major organ systems. Eventually the heart muscle is no longer able to pump enough blood to sustain life. Despite marked improvement in morbidity and mortality due to improved treatments (Cleland, et al., 2006; McAlister, Lawson, Teo, & Armstrong, 2001), congestive heart failure is the only major cardiovascular disease currently increasing in prevalence (Rosamond, et al., 2008).

CHF is responsible for over 1.1 million hospitalizations a year and more women than men are hospitalized every year as a result of CHF (Rosamond, et al., 2008).

Sudden Cardiac Death

Sudden cardiac death is the result of unexpected loss of heart function. Often referred to as sudden cardiac arrest, death occurs in close proximity to the onset of symptoms. The most common underlying cause of sudden cardiac death is coronary artery disease. Complications from CAD often lead to irregularities in the electrical impulses in the heart resulting in arrhythmias leading to asystole. Sudden cardiac death occurs more frequently in men than in women. The use of implantable defibrillators has decreased the incidence of sudden cardiac death in both men and women. Although the overall number of sudden cardiac deaths is on the decline, over 325,000 people die each year from sudden cardiac death (Rosamond, et al., 2008).

Gender Differences in Coronary Artery Disease

Although CAD remains the number one killer of both men and women, there are important gender differences in the onset, diagnosis, and progression of cardiovascular disease, particularly coronary artery disease. A number of known risk factors increase the likelihood of developing CAD: age, high blood pressure, high cholesterol, smoking, diabetes, family history of CAD, obesity and physical inactivity can all play a role in the development of coronary artery disease. The role of these risk factors may be different for men and women. For example, women receive CAD diagnoses and experience CAD symptoms on average 10 years later than men (Bello & Mosca, 2004). Also, for women

taking oral contraceptives, smoking significantly increases their risk of developing CVD (Castelli, 1999). Other important CVD risk factors, such as hypertension and diabetes, can occur during pregnancy and may predict the development of these conditions as well as cardiovascular disease later in life (Nicholson, 2007). Furthermore, the CVD mortality rate for women with diabetes is significantly higher than for men (Pilote, et al., 2007).

Diagnosis of coronary artery disease in women has a particular set of challenges. Many more women than men experience “atypical” symptoms of a cardiovascular event. Women may report dyspnoea, nausea, abdominal pain, fatigue and atypical chest pain (i.e. a sharp stabbing or pulsing pain in the chest wall, and/or a sensation of choking) when experiencing an episode of ischemia (Sangareddi, et al., 2004). Silent ischemia is more common in women than men (Lerman & Sopko, 2006). Since women might not recognize these atypical symptoms as being related to CAD or may not experience symptoms at all, their presentation to healthcare professionals can be different than men with CAD. In general women typically wait longer after symptom onset to seek medical attention than do men (Rosenfeld, Lindauer, & Darney, 2005). When women do seek medical attention for their CAD symptoms, they may be less likely to be referred for cardiac testing and less likely to receive certain CAD treatments than men (Chiaromonte & Friend, 2006; Lawlor, Bedford, Taylor, & Ebrahim, 2003; Nicholson, 2007).

Furthermore, when women are referred for cardiovascular testing the test results may have poorer diagnostic accuracy for women than for men (Mieres & Shaw, 2003; Nicholson, 2007). Exercise test are standard in the diagnosis of CAD, however younger women receive many more false positives and false negatives than men (Mieres & Shaw, 2003). Echocardiographic and radioisotope testing can be complicated by the presence of

breast tissue. Cardiovascular imaging has not been adequately linked to clinical parameters in women, making diagnosis of CAD via standardized testing methods more difficult (Mieres, et al., 2005). Coronary angiography is less useful in the diagnosis of CAD in women because women tend to have smaller coronary arteries than men and have a higher prevalence of microvascular disease (Pepine, 2004). In 2007, the American Heart Association recommended updating the guidelines for calculating Framingham risk scores for women. These recommendations attempt to take into account some of the gender differences in risk stratification for cardiovascular disease (Mosca, et al., 2007).

Some studies have shown that women are less likely to undergo percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery after acute myocardial infarction than men (Pilote, et al., 2007). Women have poorer outcomes after revascularization procedures than their male counterparts (Mieres, et al., 2005). These sex differences in rates of revascularization may be explained by disease comorbidities and other demographic variables. There are also gender differences in treatment efficacy and general cardiovascular outcomes (Rosamond, et al., 2008). It remains unclear whether various pharmacotherapy treatments have the same results in women as they do in men. Most of the large scale clinical trials of drugs used in the treatment of cardiovascular disease have greatly over-represented men in their samples, making it difficult to accurately assess the actions of these drugs in women (Nicholson, 2007). While overall life expectancy rates remain higher in women than in men with CVD, women are more likely to be hospitalized for congestive heart failure and stroke, and utilize more healthcare resources than men (Rosamond, et al., 2008). These gender disparities in life expectancy and healthcare utilization are not well understood.

Although research has clearly demonstrated that gender differences in CAD exist, the mechanism for these differences and how best to address these differences in research and clinical practice remains unclear. The effect of menopause and sex hormones on CAD is one area of ongoing study. Before menopause, the incidence of CAD in women is significantly less than in men of the same age (Bello & Mosca, 2004). Once women experience menopause their risk of developing cardiovascular disease greatly increases, and becomes similar to that of men (Pilote, et al., 2007). In addition to the gender differences in CAD symptoms, and inaccuracies in diagnostic testing, there are also gender differences in psychosocial risk factors for CAD. The prevalence of depression, a known risk factor for CAD, is higher in women than in men (Gater, et al., 1998). The epidemiological literature has shown that marriage, a form of social support, reduces the risk of death in men with CAD, but has little or no beneficial effect in women with CAD (Wiklund, et al., 1988). It is clear that gender plays an important role in the biological and psychosocial risk factors for CAD.

Psychosocial Variables and Coronary Artery Disease

In addition to the traditional health-related risk factors for cardiovascular disease, a variety of psychosocial variables play a role in the etiology, onset and progression of CAD. Over the past several decades the concept of stress and its effects on physical health has become the subject of a great deal of research. The term stress is used to describe a variety of phenomena, both in common vernacular and in the scientific community. In the early 1900s the term stress was used to describe the biological phenomena that occur when an organism is exposed to a stimulus that threatens the

homeostasis of the organism (Seyle, 1956). Since the early work on stress and stressors by Walter Cannon and Hans Selye, stress research has expanded to include both the physiological processes involved in stress and the stress response as well as the emotional and psychological aspects of stress and stressors (Mason, 1975).

The emotional and psychological aspects of stress are critical components in the link between psychosocial factors and coronary artery disease. Psychological stress, as well as physiological stress, is known to produce a variety of hemodynamic, endocrine, and/or immunologic changes within the body. It has been hypothesized that many of these stress-related changes affect the development or progression coronary artery disease. The physiological stress response can be mediated and/or moderated by psychological (e.g., coping style, personality traits, and psychological disorders) and social (e.g., social support and close relationships) processes (Rozanski, Blumenthal, Davidson, Saab, & Kubzansky, 2005).

Depression and Coronary Artery Disease

Several studies have demonstrated a relationship between depression and CAD. Recent research suggests that depression may increase the risk of developing CAD in healthy individuals; and a large body of evidence demonstrates the negative impact of depression on cardiovascular outcomes and the overall health of patients with CAD (Lett, et al., 2004). The prevalence of depression in patients with coronary artery disease ranges from 15 to 20%, which is significantly higher than the 4 to 7% estimated prevalence in the general population (Gonzalez, et al., 1996; Steffens, et al., 2000). The prevalence of depression in CAD patients is similar to that of patients with other chronic illness (Katon

& Sullivan, 1990). Depression is associated with an increased the risk of recurrent myocardial infarction, cardiac death, and/or revascularization by 2 to 2.5 fold (Horsten, Mittleman, Wamala, Schenck-Gustafsson, & Orth-Gomer, 2000; Naqvi, Naqvi, & Merz, 2005). Furthermore depression is an independent predictor of coronary artery disease in women(Clouse, et al., 2003) and in men(Ford, et al., 1998). The effects of depression on CAD outcomes are evident even when controlling of disease severity (Rutledge, Reis, Olson, Owens, Kelsey, Pepine, Reichek, Rogers, Merz, Sopko, Cornell, & Matthews, 2001). The exact mechanisms by which depression affect CAD remain unclear, although inflammatory activity, autonomic dysfunction, increased platelet reactivity, abnormal blood coagulation, endothelial dysfunction, health behavior and patient non-compliance to treatment may all play a role.

Depression has been associated with a number of CAD risk factors such as, increased use of alcohol, increased rates of smoking and decreased physical activity (Camacho, Roberts, Lazarus, Kaplan, & Cohen, 1991; Glassman, et al., 1990; Rehm, Bondy, Sempos, & Vuong, 1997). Additionally, patients with depression often fail to comply with treatment recommendations made by their physicians(DiMatteo, Lepper, & Croghan, 2000). Research has shown that post-MI patients with depressive symptomology are less likely to exercise regularly, make dietary changes and take prescribed medications after discharged compared with non-depressed post-MI patients (Lehto, et al., 2000). These lifestyle factors and issues of non-compliance associated with depression might play a large role in the relationship between depression and CAD outcomes.

There are several ways to measure depression. The most commonly utilized measures in health-related research focus on a clinical diagnosis of major depressive disorder or a measure of levels of depression symptomatology. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) is used to diagnosis a person with clinical depression, but also provides information regarding levels of depression(First, Spitzer, Gibbon, & Williams, 1996.). The Center for Epidemiologic Studies Depression Scale (CES-D) was designed to measure current levels of depressive symptoms in the general population(Radloff, 1977). Another scale commonly used to measure levels of depressive symptoms is the Beck Depression Inventory (BDI)(Beck AT, C, & M, 1961). Both the CES-D and the BDI are self-administered questionnaires and have been widely used in research. The CES-D may be more discriminating than the BDI in predicting depression among young adult populations(Santor, Zuroff, Ramsay, Cervantes, & Palacios, 1995), however both scales have been linked to cardiovascular outcomes in at risk populations(Lett, et al., 2004).

Anxiety and Coronary Artery Disease

Feelings of anxiety and anxiety disorders often co-occur with depression. Individuals reporting anxiety often express somatic symptoms such as shortness of breath, heart palpitations, and chest pain that can be mistaken for a cardiac event. However anxiety is common in patients with cardiovascular disease, and the physiological responses to anxiety may play a role in triggering adverse cardiovascular events(Januzzi, Stern, Pasternak, & DeSanctis, 2000).

Research has linked anxiety related syndromes to the development of coronary artery disease (Januzzi, et al., 2000; Kubzansky, et al., 1997; Weissman, Markowitz, Ouellette, Greenwald, & Kahn, 1990). High levels of phobic anxiety have been linked to sudden cardiac death and non-fatal myocardial infarctions in men without coronary artery disease at baseline (Kawachi, et al., 1994). Other studies have linked anxiety to adverse outcomes (e.g. fatal and non fatal cardiovascular events) in patients with established coronary artery disease (Frasure-Smith & Lesperance, 2003; Frasure-Smith, Lesperance, & Talajic, 1995; Moser & Dracup, 1996). Still many studies have failed to find an association between anxiety and coronary artery disease outcomes (Ahern, et al., 1990; Frasure-Smith & Lesperance, 1999; Hippisley-Cox, Fielding, & Pringle, 1998). And other studies have linked history of anxiety disorders to a decreased likelihood of angiographic CAD in women (Rutledge, Reis, Olson, Owens, Kelsey, Pepine, Reichek, Rogers, Merz, Sopko, Cornell, Sharaf, et al., 2001).

There are a number of instruments available to measure anxiety in populations with and without clinical anxiety disorders. Perhaps the most well known measure of anxiety is the State-Trait Anxiety Inventory (STAI), which is a self-report measure of general anxiety in both situational (state) and dispositional (trait) domains (C. D. Spielberger, Gorsuch, & Lushene, 1970). Another self-report measure used to assess avoidance related to anxiety and fear is the Fear Questionnaire (FQ) (Geer, 1965). These measures have been predominately used in young adult samples, and only recently been tested in populations of older adults. The Worry Scale (WS) was developed to address worry regarding health, social, and financial concerns in older adults (Wisocki, Handen, &

Morse, 1986). In older adult populations with and without anxiety disorders the intercorrelations among these three scales were high (Stanley, Beck, & Zebb, 1996).

Anger/Hostility and Coronary Artery Disease

Several studies have linked anger to myocardial infarction and life-threatening arrhythmias. Mittleman and colleagues (1995) showed the risk of myocardial infarction increased in the two hours following an episode of anger compared to a non-anger period. In laboratory settings, anger induction has also been shown to accelerate ventricular tachycardias and increase thresholds of the electrical termination of the tachycardias (Lampert, et al., 2007; Verrier, Dickerson, & Nearing, 1992; Verrier & Mittleman, 1996).

In addition to the induced or state anger, anger-related traits have also been associated with adverse cardiac outcomes. Healthy individuals scoring high on trait anger were at greater risk for an acute myocardial infarction than individuals scoring low on trait anger. Men trait anger was predictive of 10-year incidence of atrial fibrillation and total mortality (Eaker, Sullivan, Kelly-Hayes, D'Agostino, & Benjamin, 2004). Trait anger and hostile affect are also predictive of myocardial ischemia (Burg, Jain, Soufer, Kerns, & Zaret, 1993).

Hostility and anger are closely related constructs; hostility is generally thought of as a personality trait or stable characteristic while anger is often viewed as an emotion. Hostility has been linked to a number of adverse cardiovascular outcomes. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, young adults scoring high on measures of hostility were more likely to have coronary calcification at 10-year follow-up than those scoring low on hostility (Iribarren, et al., 2000). High levels

of hostility have also been linked to episodes of myocardial ischemia in women and men under 60 years of age(Helmers, et al., 1993). While there appears to be a dose-response relationship between hostility and CAD, the findings are not consistent across studies(Kubzansky, Davidson, & Rozanski, 2005).

Several measures of anger and hostility have been used in research with cardiac patients. The Cook-Medley Hostility Scale (Ho)(Cook & Medley, 1954) is a self-report measure derived from the Minnesota Multiphasic Personality Inventory (MMPI) constructed to measure various aspects of hostility and has been widely used in patient populations(Cook & Medley, 1954). The State-Trait Anger Expression Inventory (STAXI) is also frequently used in patient populations(C. Spielberger, 1998). This self-report measure has several subscales that address various components of anger, such as anger/in (referring to a person's tendency to suppress anger emotions), anger/out (referring to a person's tendency to direct anger towards other people or objects), and anger/control (referring to the extent to which person tries to control his/her anger expression). There is also an anger expression scale computed from the 3 subscales that evaluates a person's overall tendency to express anger. Another scale frequently used to assess hostility is the Buss-Durkee Hostility Inventory (BDHI)(Buss & Durkee, 1957). Factor analysis of this self-report measure shows two underlying constructs related to the overt expression of hostility and the experiential aspects of hostility. Studies have shown that the Ho and STAXI are highly correlated and appear to be tapping into a common variance, while the BDHI is less strongly correlated with the other scales(Bishop & Quah, 1998; Moreno, Fuhrman, & Selby, 1993).

Social Support and Coronary Artery Disease

Social support is another psychological factor that plays a role in cardiovascular disease. A lack of social support is a risk factor in for cardiovascular morbidity and mortality(Berkman, et al., 2003; Luttik, Jaarsma, Moser, Sanderman, & van Veldhuisen, 2005). The term social support is broadly used and can refer to a number of different elements of the construct of social support. Social networks (the number of people one knows, interacts with, and could reasonable rely upon), social integration (the degree to which one is a part of family, friends, and groups), and relational content (the quality and functionality of one's social relationships), may all play a role in coronary artery disease outcomes (Luttik, et al., 2005).

Patients with low levels of emotional support had higher mortality 6 months after myocardial infarction (Berkman, Leo-Summers, & Horwitz, 1992). Other research has shown that living alone and/or social isolation increases the risk of a recurrent cardiac event(Case, Moss, Case, McDermott, & Eberly, 1992; Murberg & Bru, 2001). Men may be more vulnerable to the negative effects of social isolation and have a higher risk of cardiovascular mortality and stroke associated with poor social networks(Amick, et al., 1998). In studies looking at social support in women, emotional support and perceived social support lowered the risk of cardiac events (Krumholz, et al., 1998) and the perceived impact of physical symptoms(Bennett, Baker, & Huster, 1998). More research is needed to clarify the relationship between different aspects of social support and health outcomes, however the extant literature suggests the having a strong social network is protective against adverse health outcomes in patients with coronary artery disease.

There are several different ways to measure the different aspects of social support. The Social Network Index (SNI) measures the number of significant social relationships a person has (Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997). This scale has been used in a number of studies predicting susceptibility to viral infections (Cohen, et al., 1997; Cohen, et al., 1998). The Perceived Social Support Scale (PSSS) measures the extent to which an individual perceives his or her needs are met by the social (e.g. whether the social network is providing information, support, or feedback regarding stressful situation) (Procidano & Heller, 1983). The Interpersonal Support Evaluation List (ISEL) was designed to measure the perceived availability of social resources (Cohen, Mermelstein, Kamarck, & Hoberman, 1985). Another measure of social support is the Social Support Questionnaire (SSQ) (I. G. Sarason, Levine, Basham, & Sarason, 1983). This questionnaire measures the emotional, informational, and tangible aspects of social support (Schaefer, Coyne, & Lazarus, 1981). Studies have shown that the SNI is modestly correlated with the PSSS, ISEL, and tangible aspects of social support (i.e. SSQ) (Schaefer, et al., 1981; Wills & Shinar, 2000).

Other Psychosocial Variables Related to Coronary Artery Disease

In recent years, researchers have started exploring psychological variables such as optimism and coping styles and their relationship to cardiovascular outcomes. After coronary artery bypass graft surgery, patients with high levels of optimism left the hospital sooner and had less complications than patients low on optimism (Scheier, et al., 1999). The use of different coping styles has also been shown to have an impact on cardiovascular outcomes (Gleiberman, 2007).

Overlap and Comorbidity of Psychosocial Variables and Coronary Artery Disease

As interest in the relationship between psychosocial variables and cardiovascular disease has grown, a link between a number of these variable (e.g. depression, anxiety, anger/hostility, and lack of social support) and adverse cardiovascular outcomes has become evident in the literature. In addition, many of these psychosocial variables cluster together and co-occur in the same individuals (Suls & Bunde, 2005). This line of research also raises the question of whether there is a relationship between the psychosocial variables themselves. Many of the measures of depression, anxiety and anger/hostility are moderately to strongly correlated with one another(Suls & Bunde, 2005). The commonalities and overlap of psychosocial constructs, both conceptually and in various measurement methods, is an emerging area of research.

If a relationship or even an overlap between these psychosocial variables exists, could that relationship or overlap be reasonable for the association between this variables and cardiovascular outcomes? Two studies have tried to address this question using a factor analytic approach(Boyle, Michalek, & Suarez, 2006; Frasure-Smith & Lesperance, 2003). Frasure-Smith and Lesperance followed of 896 post MI patients (232 women) for 5-year cardiovascular related mortality(Frasure-Smith & Lesperance, 2003). Measures of general health, perceived somatic symptoms, anxiety, depression, anger, and social support were collected at baseline. The State-Trait Anxiety Inventory, Beck Depression Inventory and the General Health Questionnaire (a measure of health-related quality of life) were related to disease outcome, however only depression remained significantly associated with outcome after adjusting for disease covariates. The investigators also

performed an exploratory principal components factor analysis with the psychological variables to try and assess set of underlying psychosocial factors in this data set. Three underlying factors were found; Negative Affectivity (including the BDI and STAI), Overt Anger (including the Anger Expression Scale), and Social Support (including the Perceived Social Support Scale and the number of close friends and relatives). The Negative Affectivity factor predicted cardiovascular mortality even after adjusting for depression and cardiovascular risk factors.

Boyle and colleagues (2006) examined associations of depression, anxiety, hostility, and anger in the development of coronary heart disease (CHD) in a prospective cohort study of 2015 male United States Air Force veterans. Psychosocial variables were collected at baseline using scales constructed from the Minnesota Multiphasic Personality Inventory and participants were followed for 20 years for the onset of coronary heart disease. All four psychological variables were independently associated with the development of CHD in fully adjusted Cox regression models. The researchers also examined whether any of the psychological variables were uniquely associated with CHD in a model that simultaneously tested the effects of anger, hostility, depression and anxiety. None of the variables significantly predicted incident CHD in either the age-adjusted or fully adjusted model. Additionally, Boyle and colleagues performed a principal components factor analysis on the psychosocial variables and obtained a one factor solution (comprised of anxiety, depression, anger, and hostility) which they termed “Psychological Risk Factor”. A composite score derived from the Psychological Risk Factor significantly predicted CHD in a fully adjust model. The investigators went on to refit the fully adjusted models with the individual psychological scales as predictors of

CHD and included the Psychological Risk Factor score in each model. Results showed that the Psychological Risk Factor score was a better predictor of incident CHD than any of the individual psychosocial variables.

The use of factor analytic approach to evaluate psychosocial risk factors may provide important information furthering the understanding of the role of psychosocial variables in coronary artery disease. The studies by Frasure-Smith & Lesperance, and Boyle and colleagues suggest that underlying psychological factors can be derived and used to predict the development of CHD and CHD mortality. It is not known whether these same psychosocial factor structures are evident in population of healthy women or in women with CAD, or if derived psychosocial factors will be predictive of cardiovascular events in women with coronary artery disease.

The Women's Ischemia Syndrome Evaluation (WISE) Study

The Women's Ischemia Syndrome Evaluation (WISE) Study is an National Heart, Lung, and Blood Institute-sponsored initiative designed to 1) improve the evaluation of symptoms and diagnosis of ischemic heart disease, 2) investigate the possible mechanisms for symptoms of ischemia in the absence of angiographic coronary artery stenoses, and 3) to evaluate the role of reproductive hormones on symptoms and diagnosis testing (Merz, et al., 1999). A total of 944 women with suspected coronary artery disease were enrolled from 4 different centers into the WISE study. Data from the WISE study includes demographic and clinic data, psychosocial variables, angiographic and cardiovascular disease data, and 5-year follow-up data on cardiovascular events and all-cause mortality.

There is a body of psychosocial findings related to quality of life, depression, social support and anger/hostility in the WISE data. Relevant to the proposed study, psychosocial factors (e.g., depression) were better predictors of quality of life in women with suspected ischemia than underlying CAD (Olson, et al., 2003). Women with elevated depressive symptomology and a history of depression had a higher risk clinical events and increased mortality (Rutledge, et al., 2009). In addition, lack of social support was found to predict CAD and overall mortality (Rutledge et al. 2004). Measures of hostility were predictive of mortality (Olson, et al., 2005), and anger/hostility were associated with symptoms of angina (Krantz, et al., 2006).

Summary and Study Rationale

Research has shown that there are important gender differences in the onset, diagnosis, and progression coronary artery disease. In addition to the traditional health-related risk factors for CAD, a variety of psychosocial variables (e.g., anxiety, depression, anger, hostility, social support, etc.) play a role in the etiology, onset and progression of CAD. Recent studies by Frasure-Smith and Lesperance (2003), and Boyle and colleagues (2006) suggest that analyzing the shared variance of psychosocial variables can provide additional insight into the relationship between these variables and cardiovascular event. Results from the Frasure-Smith and Lesperance (2003) study suggest that 3 psychosocial factors can be derived from multiple psychosocial scales. This body of literature suggests that analyzing derived factors and psychosocial scales together may provide more insight into cardiovascular disease risk than analyzing any one factor or psychosocial variable alone. The large number of psychosocial variables related to a variety of cardiovascular disease outcomes in the women enrolled in the

WISE study provides a unique opportunity to explore the shared variance in these psychosocial variables and assess whether an underlying psychosocial risk factor for cardiovascular disease can be identified. Therefore, the present study aims to evaluate the clustering and predictive value of multiple psychosocial risk factors of coronary artery disease in women.

Specific Aims and Hypotheses

Specific Aim 1: To determine if there is an underlying factor structure of psychosocial variables in women with suspected CAD enrolled in the WISE study.

Hypothesis 1: There will be 3 psychosocial factors in the WISE data related to the constructs of Negative Affectivity, Anger/hostility, and Social Support.

Specific Aim 2: To determine if underlying psychosocial factors are predictive of cardiovascular (CV) events in the WISE cohort.

Hypothesis 2a: Each of the derived psychosocial factor scores will independently predict CV events.

Hypothesis 2b: The combination of the derived psychosocial factor scores will be predictive of CV events in the WISE cohort.

Specific Aim 3: To determine whether the derived psychosocial factor scores predict CV events beyond traditional individual psychological predictors.

Hypothesis 3a: The Negative Affect Factor score will be predictive of CV events in addition to the predictive value of the measures of depression and anxiety.

Hypothesis 3b: The Anger/Hostility Factor score will be predictive of CV events in addition to the predictive value of the measures of anger and hostility.

Hypothesis 3c: The Social Support Factor score will be predictive of CV events in addition to the predictive value of measures of social support.

Hypothesis 3d: When analyzed together in a multivariate approach the 3 psychosocial factor scores will be predictive of CV events in addition to the predictive value of the measures of depression, anxiety, anger, hostility, and social support.

Methods

The present study uses data collected from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study (Merz, et al., 1999) to examine the clustering of psychosocial factors and their predictive value in adverse cardiovascular outcomes. WISE is a four-center study designed to evaluate the pathophysiology of coronary artery disease in women. One of the secondary goals of the WISE study is to investigate the effects of psychosocial variables in women with suspected coronary artery disease.

Study Population

Women over the age of 18 and undergoing a clinically indicated coronary angiography as part of their regular medical care were eligible to participate in WISE. Participants were recruited from 4 different sites: Allegheny General Hospital-MCP Hahnemann School of Medicine; University of Alabama at Birmingham; University of Florida, Gainesville; and the University of Pittsburgh. Women were excluded if they had any comorbidity that might compromise a one-year follow-up, were pregnant, had

contraindications to diagnostic testing, cardiomyopathy, recent myocardial infarction, congenital heart disease, congestive heart failure (New York Heart Association classification IV), or a language barrier prevented completion of questionnaire testing. Enrollment occurred in two phase; a pilot phase from 1996-1997 when 256 women enrolled and a second phase from 1997-1999 during which 680 women were enrolled. Of the consecutive women screened and found eligible, 50% agreed to participate. A total of 944 women participated in the core WISE protocol, with a subset completing site-specific protocol additions. Of the 944 women enrolled in WISE, 493 women completed the psychosocial measures of interest and are included in the present analyses¹. A smaller subset of women (N=292) completed the Spielberger Anger Expression Scale (SAES), however do to the nature of the analyses used to test the study hypotheses, results from the SAES were not included. Four of the major psychosocial variables shown in the literature to be linked to cardiovascular outcome (anxiety, depression, anger/hostility, and social support) as well as measures theoretically related to these constructs were included in the analyses. Women were excluded from the current study if they were missing a score for any of the following psychosocial questionnaire measurements: Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), Cook-Medley Hostility Inventory (Ho), Social Network Index (SNI), The Panic Attack Scale, and the Autonomic Perception Scale.

¹ The psychosocial questionnaires were added to the protocol half way through the study recruitment, therefore women recruited at the beginning of the study did not complete this part of the protocol.

Psychosocial Measures:

The Beck Depression Inventory (Beck, Steer, & Garbin, 1988) assesses the current depressive symptoms an individual has experienced over the past two weeks. The BDI is a 21-item self report measure, with each item rated on a 0-3 scale. The BDI demonstrates high internal consistency (Beck, et al., 1988) and adequate concurrent validity with clinician ratings of depression (Foa, Riggs, Dancu, & Rothbaum, 1993). It is frequently used in research conducted with patients with cardiovascular disease to assess depressive symptomology and as a proxy for a clinician diagnosis of depression.

The Spielberger State-Trait Anxiety Inventory is a twenty-item self report questionnaire that assesses anxiety in specific situations (state) and in general (trait). Participants indicate on a 1 to 4 scales how much they agree with a variety of statements aimed to evaluate an individual's feelings of anxiety. Both the state and trait versions of this scale have adequate psychometric properties (Knight, Waal-Manning, & Spears, 1983), and like the BDI, the STAI has been frequently used in patient populations.

The Cook-Medley Hostility Inventory (Ho) is a 50-item questionnaire empirically derived from the Minnesota Multiphasic Personality Inventory (Cook & Medley, 1954), which assesses a variety of components of hostility. A total of six subscales have been identified in the Ho (e.g. Cynicism, Hostile Attributions, Hostile Affect, Aggressive Responding, Social Avoidance, and Other) (Barefoot, Dodge, Peterson, Dahlstrom, & Williams, 1989). Of these subscales, Cynicism, Hostile Affect and Aggressive Responding have been linked to a variety of health outcomes, particularly in patients with cardiovascular disease (Barefoot, et al., 1989). These three subscales were used in the

current study and have been shown to have good reliability and validity(Smith & Frohm, 1985).

The Social Network Index measures the number of social roles in which an individual actively participates and therefore assesses the amount of meaningful contact with others an individual regularly engages in. The SNI consists of 12 questions which multiple parts aimed at identifying the number of people an individual has regular contact. By measuring the diversity of an individual's social network, the SNI can be used as a measure of social support. The SNI has been linked to adverse health outcomes and been used in patient populations(Cohen, et al., 1997).

Panic and autonomic perception were also assessed via questionnaire measures. Panic was assessed using a scale derived from the Body Sensations Questionnaire (BSQ)(Schmidt & Telch, 1994). The scale is a self-report measure of a variety of somatic cues and physical symptoms often associated with panic and panic disorders. Autonomic perception was measured using questions previously designed to assess to what extent an individual is aware of various autonomic processes (i.e., temperature, heart rate, etc.)(Mandler, Mandler, & Uviller, 1958).

Clinical and Cardiovascular Event Measures

Information regarding cardiovascular events was collected during the five year follow-up period. Participants were contacted annually over an average of 5.9 years to assess a variety of symptoms and outcomes. Health outcomes were verified by hospital records and/or death certificates, when possible. The 5-year cumulative withdrawal from the WISE protocol was 189 participants, with withdrawal date determined by decision of

the study nurse to close the case after giving the participant several chances to respond or trying all avenues to find the participant. The withdrawal rates were similar in the current study subsample. The outcome variable for the present study is cardiovascular events, including stroke, myocardial infarction, congestive heart failure, and death related to cardiovascular disease.

Statistical Analyses

Factor Analysis

Data were analyzed using SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL). To address the first specific aim a scale-wise principal components factor analysis with varimax rotation was conducted. The Kaiser-Meyer-Olkin measure of sampling adequacy and the Bartlett test of sphericity were used to evaluate the appropriateness of the data for factor analysis. The principal components analysis is a data reduction technique which attempts to find a linear combination of the variables that allows the maximum variance from each variable to be extracted. The variance is then removed and a second linear combination is performed to extract the maximum variances from the remaining variables. This technique allows for the analysis of common and unique variance in the data and has been used in previous research (Frasure-Smith & Lesperance, 2003). A varimax rotation was chosen to facilitate interpretation of the derived factors. This is a type of orthogonal rotation ensured that the axes are not correlated, maximizing the variance which serves to differentiated the original variables by each of the extracted factors. This makes it easier to identify each of the original variables with a single factor. A principal components analysis with oblique rotation was also performed to address the

theoretical position that the underlying factors are in fact correlated. As no substantial difference between the two rotations was noted, the varimax solution was decided upon.

The number of factors were determined using a combination of the Kaiser criterion (Eigenvalues greater than 1.0) and the more subjective method of visual inspection of the scree plot suggested by Cattell. Factor scores were derived from the varimax principal components analysis with listwise deletion of missing variables and regression variables were computed.

Regression Analyses to Predict Events

To address the second and third specific aim Cox proportional hazards regression analyses were used. Cox proportional hazards modeling is used to assess the relationship between the predictor variables and the time to the cardiovascular related outcome during the 5 year follow-up period. Kaplan-Meier survival analyses (KMSA) were not used because the KMSA approach does not allow for the effect of covariates on the function to be assessed. Cox proportional hazards modeling allows for covariates to be assessed using time to event data. The prognostic value of the factor scores alone and as a group, and in combination with the original psychosocial variables were assessed using Cox regression analyses. Six of the psychosocial scales were chosen *a priori* to be tested as predictor variables in the Cox regression analyses due to the relationships demonstrated in the literature between these variables and cardiovascular disease outcomes (Barefoot, et al., 1989; Rueda & Perez-Garcia, 2006; Suls & Bunde, 2005). These six scales: the Beck Depression Inventory, the Spielberger Trait Anxiety Inventory, the Social Network Index, and the Hostile Affect, Cynicism, and Aggressive Responding subscales of the

Cook-Medley Hostility Inventory, were further identified for *a priori* testing because they conceptually relate to the 3 factors identified by Frasure-Smith and Lesperance (2003) as well as to the factors hypothesized to be derived in the present study. Therefore the BDI and STAI were selected to represent the constructs of Negative Affectivity, the Hostile Affect, Cynicism, and Aggressive Responding subscales of the Ho were selected to represent Anger/Hostility, and the SNI was selected to represent Social Support.

Coding for the Cox regression analyses was conducted using a standard syntax provided by the data coordinating center for the WISE study. Cardiovascular events were identified, and a “time to CV event” variable was created. Deaths that were not cardiovascular in nature were recoded as missing. A total of 18 cases were dropped because of missing data. Participants who did not experience a CV event were censored at the end of the 5 year follow-up period. A total of 399 cases were censored in the analyses.

Each hypothesis was first investigated using univariate Cox regression models. Then each model was adjusted for age, smoking history, diabetes, and history of coronary artery disease (defined as greater than 50% epicardial coronary artery stenosis²). These covariates were used because of the significant relationship they have to cardiovascular disease outcomes. Additional covariates such as race, education level, and BMI were included in the Cox regression models in used to test Hypothesis 2a but were not included in further analyses because they did not change the relationships between the predictor and outcome variables. These additional covariates were dropped from the analyses both in an effort to conserve power and because further evaluation of the

² This dichotomous variable was used for history of CAD because it is the standard history of disease covariate provided with this data set. Previous results published using data from the WISE study have used this variable to account for history of CAD.

relationship of these variables and the variables of interest were beyond the scope to the present study.

Results

Sample Characteristics

A total of 493 women who completed all psychosocial measures were included in these analyses. The mean age of the women was 57 years old. The sample was predominately Caucasian (n=412), and a large majority of the participants had complete high school or higher education (n=400). Approximately 40% of the sample had coronary artery disease (n=162). At the end of the 5 year follow-up period 75 participants had experience a cardiovascular event (congestive heart failure (n=25), stroke (n=20), MI (n=20), and/or cardiovascular related death (n=9)). There were no significant difference in the demographic data between the total sample population and the subsample used in these analyses. Participant and clinical demographics are outlined in Table 1.

Hypothesis 1: Existence of Psychosocial Factors

The correlation matrix for the psychosocial variables is shown in Table 2. Almost all of the psychosocial factors are significantly correlated with one another, and most of the correlations were of moderate magnitude. This is to be expected with such a large sample size and the aforementioned conceptual overlap between the psychosocial constructs.

Next, 8 psychosocial variables (i.e., BDI, STAI, Hostile Affect, Cynicism, Aggression, SNI, Autonomic Perception, and the Panic Attack Scale) were entered into a factor analysis and the measure of sampling adequacy (Bartlett test of sphericity) for the total matrix was 0.81 ($p < 0.001$). The principal components factor analysis with a varimax rotation revealed 3 underlying factors that accounted for a total of 68% of the variance. The number of factors were determined using a combination of the Kaiser criterion (Eigenvalues greater than 1.0) and the more subjective method of visual inspection of the scree plot suggested by Cattell (See Figure 1). As hypothesized, the factor structure corresponded to the constructs of negative affectivity, hostility, and social support (See Table 3). The first factor, Negative Affectivity, was primarily composed of the BDI, STAI, Autonomic Perception, and the Panic Attack Scale, and accounted for 40.5% of the variance. The second factor, Hostility, was primarily composed of the 3 Cook-Medley subscales (i.e., Cynicism, Hostile Affect, and Aggression) and accounted for 15% of the variance. The third factor, Social Support, was almost entirely composed of the SNI, and accounted for 12.5% of the variance.

Hypothesis 2a: Individual Factors Predicting Cardiovascular Events

Regression variables were derived for each of the three factors using SPSS. This allowed for the use of factor scores in the prediction of cardiovascular events. Cox proportional hazards regressions were performed to test the hypotheses. Factor 1 (Negative Affectivity), was not predictive of cardiovascular events alone (hazard ratio (HR): 1.09, 95% confidence interval (CI) 0.88-1.36) or a model adjusted for age, smoking history, diabetes and history of CAD (HR: 1.02, 95% CI 0.82-1.30). Factor 2 (Hostility), was not predictive of cardiovascular events alone (HR: 1.15, 95% CI 0.93-

1.42) or in the adjust model (HR: 1.07, 95% CI 0.86-1.33). Factor 3 (Social Support) was significantly predictive of cardiovascular events (HR: 0.67, 95% CI 0.53-0.85), such that individuals high in the social support factor were 33% less likely to have a cardiovascular event during the 5 year follow-up period. A significant relationship remained in the adjusted model (HR: 0.78, 95% CI 0.61-0.99).

Hypothesis 2b: Combined Factors Predicting Cardiovascular Events

To assess whether the 3 factors together were predictive of cardiovascular events Cox proportional hazards regressions were performed. Although the overall model was significant ($\chi^2 [3]=13.73$, $p=.003$) the only factor to significantly predict cardiovascular events was social support (HR: 0.67, 95% CI 0.53-0.84). The overall adjusted model was significant ($\chi^2 [8]=46.61$, $p<.001$) however the addition of the 3 factors to the covariates did not reach significance ($\chi^2 [3]= 6.86$, $p=.077$ for step).

Hypothesis 3a: Cardiovascular Events Predicted by Negative Affectivity Factor, Depression, and Anxiety

In a simple Cox regression model with depression and anxiety entered simultaneously as predictor variables, Depression (HR: 1.05, 95% CI 1.01-1.09), but not Anxiety (HR: 0.98, 95% CI 0.93-1.03), was predictive of cardiovascular events. Depression became a stronger predictor when the disease covariates were added to the model (HR: 1.78, 95% CI 1.04-3.06). The hypothesis that the negative affectivity factor would be predictive of cardiovascular events beyond depression and anxiety variables was not confirmed (HR: 0.74, 95% CI 0.47-1.16).

Hypothesis 3b: Hostility Factor, Hostility Variables and Cardiovascular Events

Cox regression models were used to test the three components of Hostility (Cynicism, Hostile Affect, and Aggression) in predicting cardiovascular events. Simple Cox regression with the three subscales entered simultaneously as predictor variables showed that only cynicism (HR: 1.10, 95% CI 1.02-1.18) and hostile affect (HR: 0.81, 95% CI 0.65-0.997) were predictive of cardiovascular events. Cynicism increased the risk of a cardiovascular event by 10%, whereas hostile affect appeared to be protective against cardiovascular events, decreasing the risk by 19%. In the adjusted model, only the relationship between cynicism and cardiovascular events remained significant (HR: 1.10, 95% CI 1.00-1.16). The hypothesis that hostility factor would be predictive of cardiovascular events beyond the measures of hostility was not confirmed (HR: 0.59, 95% CI 0.21-1.63).

Hypothesis 3c: Social Support Factor, Social Networks and Cardiovascular Events

Cox regression analyses were also used to assess whether having social networks was predictive of cardiovascular events. In a univariate Cox regression, social network were associated with a 21% decrease risk of having a cardiovascular event (HR: 0.79, 95% CI 0.69-0.91). However social networks were no longer significant in the adjusted model (HR: 0.87, 95% CI 0.76-1.01). The addition of the social support factor to the Cox regression model created instability in the model due to the high correlation between the factor and the social network variable ($r=0.96$, $p<0.001$). The hypothesis that the social

support factor would be predictive of cardiovascular events beyond the social networks variable was not confirmed (HR: 0.63, 95% CI 0.27-1.50).

Hypothesis 3d: Individual Psychosocial Variables, Factors and Cardiovascular Events

Cox regression modeling was used to assess whether the combination of individual psychosocial variables was predictive of cardiovascular events. The unadjusted model with Depression, Anxiety, Cynicism, Hostile Affect, Aggression, and Social Networks added simultaneously, was significant ($\chi^2 [6]=25.81$, $p<0.001$). Social Networks (HR: 0.80, 95% CI 0.70-0.92), Hostile Affect (HR: 0.78, 95% CI 0.61-0.95), and Depression (HR: 1.04, 95% CI 1.00-1.08) were predictive of cardiovascular events, such that Social Networks and Hostile Affect were protective while Depression increase the risk of a cardiovascular event. The model remained significant with the addition of the disease covariates (Overall Chi-Square: $\chi^2 [10]=71.51$, $p<0.001$; change from previous block: $\chi^2 [6]=12.60$, $p=0.05$), however the effects of Depression (HR: 1.68, 95% CI 0.98-2.89), Hostile Affect (HR: 0.80, 95% CI 0.63-0.99) and Social Networks (HR: 0.88, 95% CI 0.67-1.01) were attenuated.

To test the hypothesis that the derived factors would be predictive of cardiovascular events in addition to the predictive value of the individual psychosocial variables, the Negative Affect, Hostility and Social Support factors were added in a third block to the above Cox regression model. The overall model remained significant ($\chi^2 [13]=79.38$, $p<0.001$) and the addition of the block with the derived factors approached significance ($\chi^2 [3]=6.28$, $p=0.10$). Given that almost all the correlations between the

individual psychosocial variables and the derived factors were significant (See Table 4), the Cox regression model with the individual variables and the factors was subject to a high degree of colinearity, making the individual hazard ratios for the final model uninterpretable. The hypothesis that the derived psychosocial factors would be predictive of cardiovascular events beyond the individual psychosocial variables was not confirmed.

Discussion

The aim of this study was two-fold: first the study was designed to evaluate whether psychosocial variables in the WISE dataset could be factor analyzed, and whether the derived factors would match the broad constructs of Negative Affectivity, Anger/Hostility, and Social Support. Secondly, the study aimed to evaluate the clustering and comorbidity of psychosocial variables (both as factors and in a multivariate approach) and the prediction of cardiovascular events in a population of women with suspected coronary artery disease.

Previous research has found psychosocial factors within larger data sets(Boyle, et al., 2006; Frasure-Smith & Lesperance, 2003). Results from this study show that factors can be derived from the psychosocial variables in the WISE study. In support of the first hypothesis, three psychosocial factors were found. These factors corresponded with the broader constructs of Negative Affectivity, Hostility, and Social Support. Cox regression analyses revealed that the Social Support factor (consisting primarily of the SNI) was protective of CV events, however Factor 1 and 2 (Negative Affectivity and Hostility) were not independently predictive of CV events. The individual psychosocial variables of

low social networks (SNI), low hostile affect (Cook-Medley Hostile Affect), and high depressive symptomology (BDI) were independently predictive CV events.

Factor 1: Negative Affectivity

Negative Affect is often conceptualized as a personality trait where an individual is more likely to experience negative emotions. While an individual with negative affect is not necessarily depressed, he or she may be more likely to suffer from depression or endorse measures of depressive symptomology than individuals who do not have negative affect. An individual with negative affect would also be more likely to experience other “negative” emotions related to feelings of anxiety, doubt or fear. A total of 4 measures related to negative affectivity loaded highly onto Factor 1, and therefore this factor was labeled “Negative Affectivity”. Not surprisingly, the measures of depression (the BDI) and anxiety (the STAI) loaded highly. The Panic Attack Scale, which may be conceptually linked to feelings of anxiety and negative emotions also loaded highly on this factor. The fourth measure to strongly load on this factor was the Autonomic Perception Scale. Individuals reporting acute awareness of autonomic activities, specifically physical changes (often interpreted as symptoms) score highly on the Autonomic Perception Scale. Autonomic perception is associated with the personality trait Neuroticism. Some researchers have linked Negative Affect and Neuroticism, showing that individuals high on Neuroticism also score highly on Negative Affect (Rusting & Larsen, 1997). The results of this factor analysis suggest that the psychological constructs of depression, anxiety, panic, and neuroticism (by extension of autonomic perception) overlap, or cluster as a Negative Affectivity factor.

Factor 2: Hostility

Although previous research on the Cook-Medley Hostility Inventory used a factor analytic approach to identify the subscales used, these 3 subscales were more similar to each other than they were to any of the other psychosocial variables used in this study. Therefore it was not surprising that the 3 subscales of the Cook Medley Hostility Inventory hung together in the factor analysis as psychosocial Factor 2. The subscales Cynicism, Hostile Affect and Aggressive Responding are conceptualized as components of the larger construct of hostility. Barefoot and colleagues (1989) defined hostility as “a broad psychological domain encompassing various cognitive, emotional, and behavioral aspects of an individual’s orientation towards interpersonal transactions.”(Barefoot, et al., 1989). In the exploratory factor analysis conducted by Frasure-Smith and Lesperance (2003), measures of hostility as well as anger measures clustered together to form a factor. The current study was unable to include measures of anger in the factor analysis because these measures were only available in a small portion of the sample (n=292). Despite the lack of anger measures, the existence of a hostility factor supports previous findings in this field.

Factor 3: Social Support

Social support has been linked to positive health outcomes in a growing body of research. Factor 3 (Social Support) extracted in this study was composed almost entirely of the Social Network Index. Although the Social Support factor derived in analyses by Frasure-Smith and Lesperance (2003) had three items load on to it (the Perceived Social

Support Scale, number of close relatives, and number of close friends), two of these items (number of close friends and number of close relatives) are included in the Social Network Index. These analyses also revealed that the Social Support factor was negatively correlated with the BDI, STAI and the Cook-Medely; something that is supported conceptually as individuals having high levels of depression, anxiety, and hostility would be less likely to have high levels of social support. Social Networks and Social Support may be more accurately conceptualized as positive psychology variables. Since the other variables analyzed in this study were more traditional or “negative psychology” variables, it is not surprising that this construct would separate out during factor analysis. The current finding of a Social Support factor, distinct from other psychosocial variables, confirms findings from earlier research (Frasure-Smith & Lesperance, 2003).

Existence of Psychosocial Factors

The current study supports previous findings that psychosocial factors can be derived from groups of psychosocial variables. The three factors derived in this population of women with suspected myocardial ischemia mirror the factors derived in a population of predominantly men with coronary artery disease (Frasure-Smith & Lesperance, 2003). The current study and the study conducted by Frasure-Smith and Lesperance did not use all of the same scales to measure the same psychosocial variables. Both studies used the BDI to measure depression and the STAI to measure anxiety (although the current study used the trait version, whereas Frasure-Smith and Lesperance used the state version of this scale); however different scales were used to

measures anger/hostility, social support, and physiological response/symptom reporting. The fact that the present study found similar factors to the previous study despite using different measures points to the existence of overlap between the various psychosocial measures. It further suggests an overlap of psychosocial constructs, which maybe as important to evaluate as the unique aspects of the individual constructs.

Factors Predicting Cardiovascular Outcomes

The second set of hypotheses predicted that the derived psychosocial factors would predict cardiovascular events. Neither the Negative Affectivity factor nor the Hostility factor was predictive of cardiovascular outcomes. Unlike previous studies which found Negative Affectivity factor and a Psychological Risk Factor (containing measures of depression, anxiety, anger and hostility) (Boyle, et al., 2006; Frasure-Smith & Lesperance, 2003) predictive of increased likelihood of cardiovascular events, neither factor reached statistical significance in WISE. There are several possible explanations as to why the current study was unable to replicate the previous findings. First, this was a sample of women with suspected coronary artery disease, which may have accounted for the number of cardiovascular events in this population being relatively low (n=75, 15% of the sample). Secondly this sample consisted of women with suspected CAD. The other study samples were predominantly male (Barefoot, et al., 2000; Boyle, et al., 2006; Frasure-Smith & Lesperance, 2003). Gender may be a moderating factor in deleterious relationship previously established between Negative Affectivity, anger/hostility and cardiovascular disease.

Women might be less susceptible to these particular psychosocial risk factors than men. Furthermore, previous literature has shown that women are more likely to utilize health care services(Bertakis, Azari, Helms, Callahan, & Robbins, 2000) and receive preventive care(Cleary, Mechanic, & Greenley, 1982) than men. Women also report more general somatic symptoms than men and are more likely to seek medical attention for these symptoms(Ladwig, Marten-Mittag, Formanek, & Dammann, 2000). In this study the autonomic perception scale loaded highly on the negative affectivity factor (high scores on the scale were positively correlated with depression, anxiety, and hostility). Increased autonomic perception may lead to more symptom reporting which may lead to women seeking and receiving more preventive, ultimately reducing the number of cardiovascular events in this population.

Only one factor, evidenced a significant relationship with cardiovascular events. Social Support significantly reduced the likelihood of having a cardiovascular event in this population. Although, Frasure-Smith and Lesperance(Frasure-Smith & Lesperance, 2003) did not find their Social Support factor to be significantly predictive of cardiovascular events, other research has shown that high levels of social support and larger social networks are protective against adverse health outcomes(B. R. Sarason, Sarason, & Gurung, 2001). As mentioned previously, the Social Support factor derived by Frasure-Smith and Lesperance (2003) utilized different measures of social support, which may account for the difference in their findings from those in WISE. Gender differences have been found in social support and health outcomes(Shye, Mullooly, Freeborn, & Pope, 1995). The protective role of social support may be more pronounced

in a sample of women, which could account for the positive findings presented in this study.

Individual Psychosocial Variables vs Psychosocial Factors

The second set of hypotheses was aimed at evaluating the individual psychosocial variables Depression, Anxiety, Hostility and Social Networks, and their relationship to cardiovascular events and to the derived factors. This studies findings that depression was predictive of cardiovascular events(Frasure-Smith & Lesperance, 2003, 2008; Lett, et al., 2004) and that social networks reduced the risk of cardiovascular events is supportive of the(Friedland & McColl, 1987; Gliksman, Lazarus, Wilson, & Leeder, 1995; Murberg & Bru, 2001) previous literature. This study also found that high levels of Cynicism were predictive of cardiovascular events; a finding also supported in previous research(Chaput, et al., 2002). Although these findings were not surprising, the results of this study extend the depth of the literature to a population of women.

The literature regarding the effects of Hostile Affect on cardiovascular outcomes has been mixed(Barefoot, Larsen, von der Lieth, & Schroll, 1995; Boyle, et al., 2004; Hearn, Murray, & Luepker, 1989). Although most of the previous research has found no relationship between hostility and hostile affect of have found it to be predictive of cardiovascular events; few studies have found anger(Eng, Fitzmaurice, Kubzansky, Rimm, & Kawachi, 2003) or hostility to be protective against cardiovascular outcomes.

The results of this study suggest that Hostile Affect, when entered alone and simultaneously into a Cox regression model with other psychosocial variables, is protective against cardiovascular events. As the direction of the relationship between

Hostile Affect and CV events is the same in both univariate and multivariate models, issues relating to suppressor variables and/or multicollinearity may be ruled out as an explanation for this finding. Most of the previous research has been conducted in men. This may suggest that the mechanisms through which hostile affect act on cardiovascular disease differ by gender. Research has shown that “Anger-In” increases the risk of cardiovascular events in men and women (Eaker, et al., 2004; Haynes, Feinleib, & Kannel, 1980). However, there is presently no information to assess whether Anger-In and low Hostile Affect are correlated. Women who suppress negative emotions while in conflict with their spouse had a higher mortality rate than women who did not (Eaker, Sullivan, Kelly-Hayes, D'Agostino, & Benjamin, 2007). It is possible that it is the suppression of hostile affect and negative emotions that is deleterious to women’s health and not the emotions themselves. Perhaps, being able to recognize and endorse hostile affectivity is protective as it allows for the expression of these emotions and a subsequent decrease in the physiological stress responses associated with keeping such emotions suppressed.

A Multivariate Approach

One of the most intriguing results of the study was the multivariate Cox regression analysis conducted to address hypothesis 3d that the three psychosocial factors combined would be predictive of CV events beyond the measures of depression, anxiety, anger, hostility, and social support. Despite the limitations previously discussed with the addition of the last block of the model, the results are intriguing. After controlling for the disease covariates, the addition of the individual psychosocial variables as a second block was significantly predictive of cardiovascular events. This multivariate approach to

assessing individual psychosocial variables has seldom been attempted in the existing literature. Most researchers assess only one or two psychosocial variables of interest in their analyses. That this step of the model is significant, suggests that there is predictive utility in assessing a variety of psychosocial variables with a known relationship to cardiovascular disease together, rather than separately. Although the addition of the block of derived factor scores was not significant ($p=0.10$), the notion of a psychosocial factor approach to predicting cardiovascular events warrants further investigation.

The fact that the independent psychosocial variables were able to be factor analyzed into factors supports the idea that there is shared variance among these independent constructs, or at the very least, among the measurements of these constructs. When the results of the multivariate analysis are taken into consideration, the results of this study suggest that a multivariate approach, and/or a factor analytic approach may be more valuable than assessing individual psychosocial risk factors. By assessing multiple psychosocial factors at once, it is possible to draw a more complete picture of the contribution of psychological constructs in the progression cardiovascular disease. Individual assessment is unable to take into account both the unique and shared variance of psychosocial variables. Just as various physiological risk factors are important to assess in combination when evaluating cardiovascular disease risk because of the increased risk certain combination of these physiological factors confer (e.g., hypertension and diabetes), combinations of certain psychosocial factors may act in a similar manner and should therefore be evaluated in a similar way.

The Importance of the Clustering Approach

Looking at how various psychosocial variables cluster together is not a new approach. Decades of research on personality have looked at how various traits cluster together to form distinct personality types. Early research on personality connected individuals who were hard-driving, competitive, pressed for time, hostile, and had vigorous voice characteristics as demonstrating Type A personality (Friedman & Rosenman, 1959). This personality type was linked to cardiovascular disease (Brand, Rosenman, Sholtz, & Friedman, 1976). As the field continued to develop, investigations into the individual components of Type A personality lead to the findings that the traits of anger and hostility were driving the association between this personality type and cardiovascular disease outcomes (Dembroski, MacDougall, Williams, Haney, & Blumenthal, 1985; Schwalbe, 1990). Research continues today on personality types and their relationships to disease (Denollet, 1998; Denollet & Brutsaert, 1998). This research allows for the evaluation of clusters of personality traits and disease outcomes. The results of the current study suggest that there is utility in evaluating clusters of psychosocial variables beyond a simple personality type approach. Assessing a wide range of psychosocial variables connected to cardiovascular disease outcomes provides a more complete picture of psychosocial risk.

Study Strengths and Limitations

One of this study's greatest strengths may also be considered a limitation. This study was conducted in a population of women with suspected coronary artery disease.

The current findings may not be generalizable to other populations. There are noted gender differences in cardiovascular disease research and as a result these findings may have limited generalizability to a similar population of men. However, few research studies have focused solely on women and the results of this study are an important step towards filling the gender gaps in the literature.

Another limitation of this study was the lack of positive psychology measures included in the data analysis. Because this study utilized previously collected data, measures of positive psychology (such as optimism and coping) and additional measures of social support could not be added to analyses. It is unclear whether the factor structure found in the WISE data would be similar if such measures were included. One study conducted by Martens et al. (2007) included measures of Positive Affect in a principal components analysis and derived 4 factors: depressed affect, anxious apprehension, positive affect, and emotional exhaustion (Martens, Smith, & Denollet, 2007). If additional measures of social support or positive affect were included in the WISE factor analysis, a 3 factor solution with Positive Affect loading on the Social Support factor, or a 4 factor solution with a separate positive affect factor could be expected. Without the addition of positive psychology measures, it is unclear as to whether the range of psychosocial variables is adequately represented in the results of this factor analysis.

The other major limitation of this study is in the data analytic strategy and the number of cardiovascular events recorded in this population. Since a principal components analysis is considered a data reduction technique, the derived factors are highly correlated with the scales from which they were derived. This makes it impossible to evaluate the hypothesis that the 3 psychosocial factors combined would be predictive

of CV events beyond the measures of depression, anxiety, anger, hostility, and social support without creating instability in the Cox regression model due to colinearity. A principal axis factoring approach may have been more appropriate as it does not simply reduce the data but allows for the derivation of underlying factors if they exist. A principal axis factoring approach was not chosen in order to replicate the techniques currently used in the literature (Boyle, et al., 2006; Frasure-Smith & Lesperance, 2003; Martens, et al., 2007).

Finally, the current study was underpowered for the hazard ratios attained. According to the methodology proposed by Hsieh & Lavori (2000) which allows for the calculation of sample size in Cox regression models that use non-binary covariates (previous methodology only allowed for calculation of sample size in Cox regression using binary covariates), the number of events observed in this study was inadequate. When performing a multivariate Cox regression, adjusting for covariates that explain 30% of the variance in the outcome variable requires a total of 108 events/endpoints (as the number of endpoints should be inflated by $1/(1-.3)$). The current analyses had 75 events, leaving them underpowered for hazard ratios under 1.3. Since hazard ratios typically found in psychology, as well as in this study, are smaller than 1.3, the power to accurately detect a relationship between the variables and cardiovascular outcomes was reduced. This may explain why the present study was unable to replicate the relationship between negative affectivity and cardiovascular events found in the Frasure-Smith & Lesperance (2003) study.

Future Directions

The results of this study suggest the existence of shared variance between individual psychosocial variables. Additionally, the results suggest that evaluating the shared variance of these psychosocial variables in a multivariate approach or by use of derived psychosocial factors provides valuable information in the prediction of cardiovascular events in women with suspected coronary artery disease. Future research should seek to replicate these findings in more diverse populations.

The existence of underlying psychosocial factors should be evaluated using a principal axis factoring approach. This data analytic approach focuses on the shared variance that exists between each of the individual measures and extracts a small set of latent variables within the data. This technique would allow for the evaluation of the questions raised by the current study: are individual psychosocial constructs and their measures related? Using a principal axis factoring approach would also allow for the evaluation of the hypothesis that the 3 psychosocial factors combined would be predictive of CV events beyond the measures of depression, anxiety, anger, hostility, and social support without creating instability in the Cox regression model.

Finally, the results of this study bring to light the possibility of creating a Psychosocial Risk Score for cardiovascular disease, much like the Framingham Risk Score. The Framingham Study is one of the most famous epidemiological health studies of the 20th century. It began in 1948, in Framingham, Massachusetts, following healthy men and women residing in the town (Kannel, McGee, & Gordon, 1976). Results from this landmark study revealed a number of different biological risk factors that could be

used to predict a healthy individual's risk of developing cardiovascular disease over a given time period. The Framingham Risk Score uses various risk prediction algorithms based on a wide range of physiological factors allowing for the prediction of different cardiovascular disease outcomes (Pinsky, et al., 1985). The original Framingham Risk Scores were developed using multiple logistic formulations (newer versions utilize Cox regression models) that estimate the conditional probability of a cardiovascular event for any set of risk factors (x), using the actual level of each factor, their regression coefficients (b) and the constants for the intercepts (Kannel, et al., 1976). Utilizing risk functions in this manner has revolutionized screening methods in primary care medicine. Simple biological markers collected during an office visit can be plugged into the algorithm to obtain a risk score which physicians can then use to help make decisions regarding further testing and recommendation for behavioral interventions. The results of the present study suggest that it might be possible to create an algorithm based on various psychosocial factors that can be used to predict risk of cardiovascular events. This Psychosocial Risk Score could be equally as valuable to a clinician. When used in conjunction with the Framingham Risk Score a Psychosocial Risk Score could be useful in evaluating increased risk of cardiovascular events, as well as helping clinicians identify patients for which psychological intervention could be beneficial. Evaluating a variety of psychosocial variables in patients with coronary artery disease could lead to a better understanding of how psychosocial variables affect the progression of cardiovascular disease and ultimately lead to innovative interventions for cardiac patients.

Table 1: Participant Demographics

Participant Characteristics	Study Sample n=493	Total Sample n=944
Age (years)	57.6 ± 11.4	58.3 ± 11.4
Race		
African American	77 (15.6%)	164 (17.4%)
Non-Hispanic White	412 (83.6%)	767 (81.1%)
Other	4 (0.8%)	13 (1.4%)
High School Graduate or above	400 (81.1%)	744 (78.6%)
Income		
unknown	39 (7.9%)	75 (7.9%)
less than \$20,000	161 (32.7%)	315 (33.3%)
\$20,000-\$34,999	98 (19.9%)	201 (21.2%)
\$35,000-\$49,999	103 (20.9%)	165 (17.4%)
\$50,000-\$99,999	73 (14.8%)	129 (13.6%)
greater than \$100,000	19 (3.9%)	36 (3.8%)
History of Smoking	246 (49.9%)	501 (52.9%)
History of Hypertension	283 (57.4%)	558 (58.9%)
History of Diabetes	114 (23.1%)	236 (24.9%)
History of Dyslipidemia	256 (51.9%)	479 (50.6%)
Average Resting Heart Rate	73.7 ± 12.5	73.5 ± 12.5
BMI	29.3 ± 6.2	29.4 ± 6.3
History of Cardiovascular Disease*	162 (39.2%)	364 (38.4%)
Cardiovascular events**	75 (15%)	169 (17.8%)

* ≥ 50% stenosis of any coronary vessel

** Incident Stroke, MI, CHF, Death

Table 2: Correlation Table of Psychosocial Variables

	CM Cynicism	CM Aggression	CM Hostile Affect	Panic Attack Scale	Spielberger Trait Anxiety	Autonomic Perception	BDI	SNI
CM Cynicism		.394**	.511**	.316**	.367**	.277**	.334**	-.166**
CM Aggression			.375**	.196**	.147**	.149**	.180**	-.038
CM Hostile Affect				.264**	.393**	.291**	.361**	-.121**
Panic Attack Scale					.497**	.392**	.516**	-.051
Spielberger Trait Anxiety						.446**	.689**	-.172**
Autonomic Perception							.484**	-.047
BDI								-.164**

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Table 3: Component Matrix From Factor Analysis with Varimax Rotation^a

	Components		
	Factor 1 Negative Affectivity	Factor 2 Hostility	Factor 3 Social Support
CM Cynicism	.290	.724	-.187
CM Aggression	-.003	.820	.086
CM Hostile Affect	.301	.720	-.089
Panic Attack Scale	.724	.173	.061
Spielberger Trait Anxiety	.812	.179	-.207
Autonomic Perception	.721	.114	.116
BDI	.807	.171	-.210
SNI	-.045	-.073	.964

Abbreviations: CM, Cook Medley; BDI, Beck depression inventory; SNI, Social Network index

a. Rotation converged in 4 iterations.

Table 4: Correlation Table of Psychosocial Variables and Derived Factor Scores

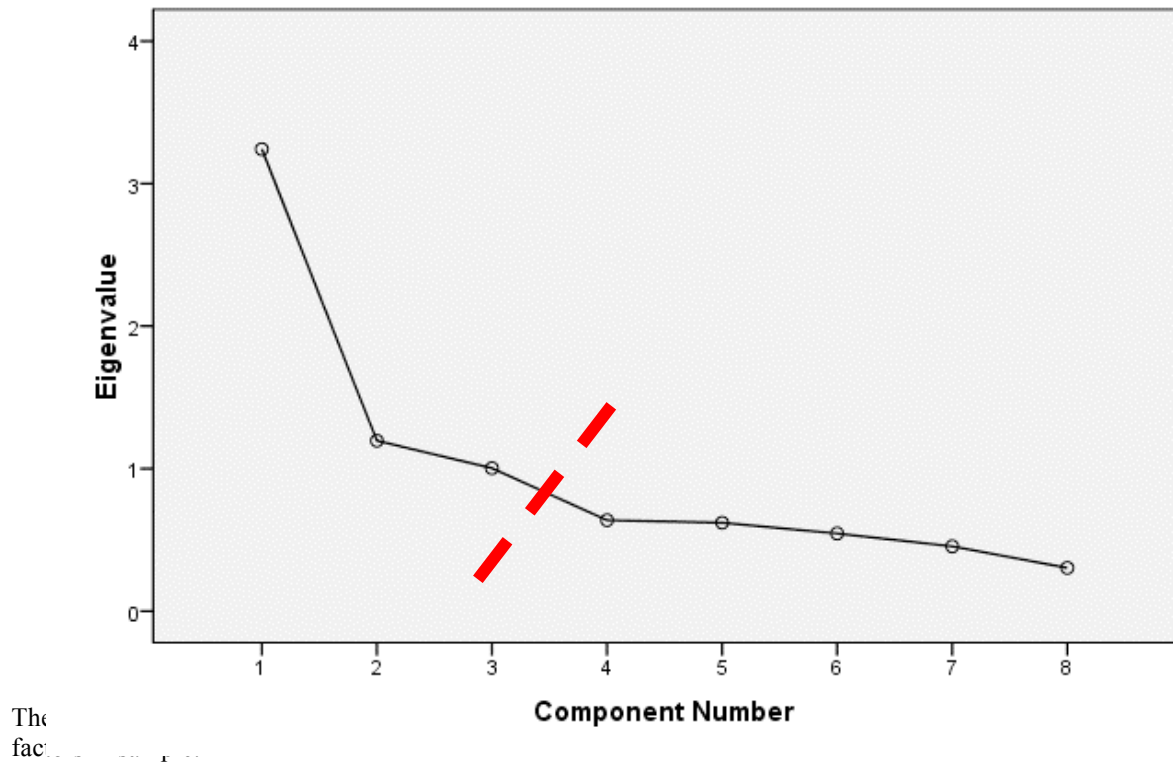
	CM Cynicism	CM Aggression	CM Hostile Affect	Panic Attack Scale	Spielberger Trait Anxiety	Autonomic Perception	BDI	SNI	Negative Affectivity Factor Score	Hostility Factor Score	Social Support Factor Score
CM Cynicism		.394**	.511**	.316**	.367**	.277**	.334**	-.166**	.283**	.732**	-.163**
CM Aggression			.375**	.196**	.147**	.149**	.180**	-.038	.010	.819**	.102*
CM Hostile Affect				.264**	.393**	.291**	.361**	-.121**	.304**	.720**	-.087
Panic Attack Scale					.497**	.392**	.516**	-.051	.735**	.175**	.070
Spielberger Trait Anxiety						.446**	.689**	-.172**	.804**	.177**	-.193**
Autonomic Perception							.484**	-.047	.724**	.130**	.107*
BDI								-.164**	.822**	.164**	-.169**
SNI									-.038†	-.062†	.963**
Negative Affectivity										.006†	.016†
Hostility											.013†

**Correlation is significant at the 0.01 level (2-tailed)

* Correlation is significant at the 0.05 level (2-tailed)

† Varimax rotations forces a solution that maximizes the variance of each factor while minimizing the variance around it factor, in an effort to achieve uncorrelated factors from clusters of variables. Although the correlation coefficients for the three factors are not zero, they are very small and not statistically significant, showing that the factors are not correlated with each other. The small correlation coefficients that are derived for these factors are most likely due to noise in the data or reflect the fact that the many of variables making up the different factors are significantly correlated with each other. When the separate clusters of variables are correlated with each other a true zero-correlation of the derived factor scores may not be achieved through varimax rotation(Rummel, 2002).

Figure 1: Scree Plot From Principal Component Analysis



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